Timing of Repeated Lactate Measurement in Patients With Septic Shock at the Emergency Department

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ABSTRACT

Background: The objective of this study was to evaluate the prognostic value of lactate levels during the first 12 hours after shock development and to identify the optimal timing for repeated lactate measurements in patients with septic shock.

Methods: We conducted a retrospective cohort study using a prospective data registry, and enrolled 2,226 consecutive adult patients with septic shock between January 2010 and December 2015. Blood lactate was measured at shock development, and after 2, 4, 6 and 12 hours (T_0, T_2, T_4, T_6 and T_{12}) during protocol-driven resuscitation bundle therapy. The prognostic value of lactate levels for 28-day mortality was analyzed using logistic regression and receiver operating characteristic curve analysis.

Results: A total of 829 patients with septic shock were included in the study, among whom 211 died during the study period. The lactate levels at each time point were associated with increased 28-day mortality, and the lactate level at 6 hours had the greatest prognostic value (area under the curve of $T_0 = 0.61$; $T_2 = 0.65$; $T_4 = 0.69$; $T_6 = 0.72$ and $T_{12} = 0.62$, and odds ratio (OR) of T_0, 1.17 [95% CI: 1.11-1.23]; T_2, 1.23 [95% CI: 1.17-1.30]; T_4, 1.30 [95% CI: 1.22-1.38]; T_6, 1.33 [95% CI: 1.26-1.42] and T_{12}, 1.24 [95% CI: 1.19-1.30]). Hyperlactatemia over 2 mmol/L and 4 mmol/L at 6 hours from shock was associated with 4-times higher mortality (≥2 mmol/L, OR = 3.89 [95% CI: 2.48-6.09]; ≥4 mmol/L, OR = 3.93 [95% CI: 2.83-5.44]).

Conclusions: During the first 12 hours following shock development, the optimal time point of repeated blood lactate measurement was 6 hours, which was the greatest prognostic value for mortality.

Key Indexing Terms: Sepsis; Shock; Mortality; Lactic acid; Prognosis. **[Am J Med Sci 2018;356(2):97–102.]**

INTRODUCTION

Lactate is a physiologic marker of oxygen balance that has prognostic value for mortality in septic patients.[1-4] Lactate >4 mmol/L is the clinical parameter defining tissue hypoperfusion in sepsis, and the association between high blood lactate concentrations and increased mortality is already well-known.[5,6] Although tissue hypoperfusion may be the most common cause of initial hyperlactatemia, there are also other contributing factors such as aerobic glycolysis, coexisting acidemia and drugs.[2,7] Therefore, repeated blood lactate level measurement after protocol-driven resuscitation bundle therapy can serve as a surrogate for response to therapy and may be more predictive for mortality than the initial lactate value.[8-10] The current surviving sepsis guideline recommends that measurement of lactate level on initial presentation and repeated measurement within 6 hours if the initial lactate level is elevated.[5] However, no study following the release of the new definition of septic shock [sepsis-3] has yet examined which measurement time point from the development of shock provides the most important prognostic value of lactate in the emergency department (ED) in patients with septic shock receiving protocol-driven resuscitation bundle therapy.[11]

The objective of this study was to evaluate the prognostic value of lactate levels during the first 12 hours after shock development and to

identify the optimal timing for repeated blood lactate measurement in patients with septic shock defined as sepsis-3.

METHODS

Setting and Population

This retrospective cohort study of a prospective data registry was performed at an urban academic adult ED at a tertiary referral center with an annual census of more than 100,000 patients in the Republic of Korea. The study received patients' informed consent and was approved by the Research Ethics Committee of the hospital.

Between January 2010 and December 2015, a total of 2,226 consecutive adult patients (≥18 years of age) were prospectively entered into the septic shock registry. Septic shock was defined as refractory hypotension, systolic blood pressure <90 mm Hg or mean arterial pressure <70 mm Hg requiring vasopressors, despite adequate fluid therapy, or a blood lactate concentration of at least 4.0 mmol/L in patients with infection.[5] In the present study, we included 1,515 patients meeting the newly released septic shock definition who had received vasopressors and who had initial lactate levels over 2.0 mmol/L after adequate fluid therapy. Exclusion criteria were anyone of the following: patients with "do not attempt resuscitation" status, patients who were transferred to another hospital during initial resuscitation and patients who lacked data for repeated lactate measurement.

All patients with septic shock were treated with protocol-driven resuscitation bundle therapy, including early goal-directed therapy, antibiotics, vasopressors, lung-protective ventilation, glucocorticoids, and surgical intervention if indicated.[5] All enrolled patients were managed in the ED at least 6 hours and then transferred to the intensive care unit. Lactate concentrations were measured at septic shock development and again at 2, 4, 6 and 12 hours after the initial measurement (T_0, T_2, T_4, T_6 and T_{12}).

Data Collection

Demographic and clinical data, including age, sex, symptoms, previous medical history, initial vital signs, severity, and laboratory values on admission, were retrieved from the septic shock registry. The sequential organ failure assessment score was calculated in the ED at the time of development of septic shock.[12] The primary clinical outcome of this study was 28-day mortality.

Statistical Analysis

Continuous variables were expressed as means and standard deviations or as median and interquartile range (IQR) if the assumption of a normal distribution was violated. Categorical variables were expressed as numbers and percentages. To compare baseline characteristics and laboratory examination values between the survivor and nonsurvivor groups, Student's *t*-test was employed to compare the means of normally distributed continuous variables, whereas the Mann-Whitney *U*-test was used to compare noncontinuous variables. The chi-squared or Fisher's exact test was used to compare categorical variables.

To evaluate longitudinal change and profiles of the repeated measurements of lactate levels at baseline, 2, 4, 6 and 12 hours, we applied multilevel mixed effects modeling. For repeated measurements of lactate levels, we conducted repeated measures analysis of variance to evaluate differences in lactate levels over time, mortality and the interaction of time and mortality. As the study included retrospectively collected data, there were several missing values for lactate levels at 2-12 hours (approximately 25% of data). The missing values were imputed using interpolation of 2 adjacent observed data of the missing value and using extrapolation of 2 previously observed data points. The optimal timing of lactate level measurement was evaluated using logistic regression modeling and receiver operating characteristic (ROC) curve analysis in a univariate model. The model performance was evaluated using the area under the curve (AUC) of ROC curves and the cut-off value for the prediction model was determined with the Youden index. All tests in the study were 2-sided and $P < 0.01$ was considered statistically significant. All statistical analyses were performed using SPSS for Windows version 20.0 (SPSS Inc., Chicago, IL).

RESULTS

Patient Characteristics

Of the 1,515 adults patients diagnosed in the ED with septic shock according to the new sepsis-3 definition during the study period, we excluded 149 patients withdrawn from protocol-driven resuscitation bundle therapy owing to transfer to another hospital, 369 patients with "do not attempt resuscitation" status, and 168 patients who had no repeated measurements of lactate after the initial measurement, leaving 829 patients who were enrolled in the study. The mean patient age was 64.9 years, and 509 patients (61.4%) were men. Overall, 618 patients survived and 211 patients died, yielding a 28-day mortality rate of 25.5% (Figure 1).

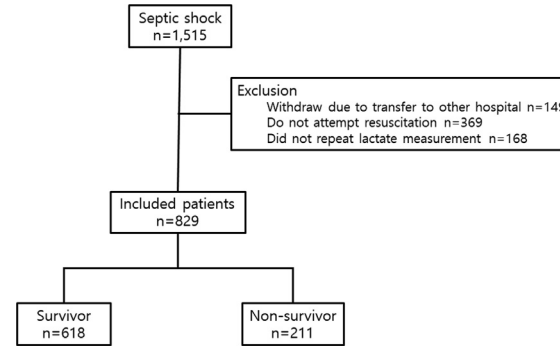

FIGURE 1. The flow diagram of participants.